surgical option down the road in a positive or negative effect?

DR. ALVAREZ: Dr. Wright, the answer to your first question is in our initial pilot study, I actually had a patient who had had previous surgery. It was an endoscopic release and he was quite unsuccessful. He was still having quite a bit of pain. That OssaTron treatment on him, in three months, he was basically pain-free.

As far as it interfering with future surgery, the thing, as a treating foot and ankle orthopedist, and I can tell you that I see my share of heel pain, as I am sure that Dr. Pfeffer and you see in your practice of foot and ankle, is it actually will give me an opportunity to treat a patient and virtually do minimal or no harm.

The question then becomes, well, what is the level of activities of daily living for these people that come in that cannot go back to work. They work on concrete floors. All of a sudden, for my practice, I potentially have something to offer these people.

Now, to put this in perspective. When HealthTronics asked me to do the pilot study, I was very skeptical. My first five patients I treated, I did not treat any further than that until I saw that the result was tending to be.

What that is going to do for my practice, if the

OssaTron is released, it is going to give me a treatment that I can give at about six months for somebody that comes in and tells me that, "I can't stand this pain anymore. You have done night splints. You have done injections. You have done arch support. You have changed my shoes. I just can't continue to move around."

All of a sudden, I can have something to offer these people and we hear it. It is very frustrating.

Thank you.

DR. BOYAN: Dr. Pfeffer?

DR. PFEFFER: I have several very brief questions. First, how was the rupture of plantar fascia diagnosed in the two cases that you have?

DR. OGDEN: Obviously, initially by history and physical examination. And we documented it with MRI.

DR. PFEFFER: Did you look at the effect of prior cortisone injections as a predictor of success?

DR. OGDEN: We divided out the treatment groups by each group having had cortisone injections. We didn't specifically look whether or not the prior cortisone injection might have affected the OssaTron treatment, itself. No; we did not do that.

DR. PFEFFER: Did you analyze patient weight as a covariate?

DR. OGDEN: No.

DR. PFEFFER: How did you establish sensitivity and reproducibility of the dolorimeter test?

DR. OGDEN: We did not specifically test that with reproducibility. The way it was done, the device was placed against the patient's heel until they experienced the pain that they had in the morning. That number was recorded and, on each successive evaluation, we pushed the palpometer, the dolorimeter, to that number and asked the patient, then, to give us their VAS scale on a 1 to 10.

It is a very simple device. I don't think there is an easy way to quantitate it.

DR. PFEFFER: I thought that was very fair, personally, but I just wasn't familiar with the device, so I just wanted a little more information.

A couple of other quick issues. Would you object, or would the company object, to the term, as the panel has been asked, of plantar fasciitis or, more specific, proximal plantar fasciitis to replace the term heel-pain syndrome in the diagnosis and treatment.

DR. OGDEN: I should probably defer to Ms. Marlow on that. I am not sure.

MS. MARLOW: When we first submitted the feasibility study IDE, and several supplements afterward, this was one of the most contentious topics we had. Unfortunately for the division we are working with, we also

had changing medical officers we were working with. The definition changed every time.

We have no objection whatsoever to changing. Actually, as I tried to allude to during my presentation, we finally ended up using your definition, or the definition in the textbook that you wrote the chapter for.

DR. PFEFFER: I am honored, but that was ten years ago and I, personally, have changed the way I look at this. Again, it is just a semantic issue. You treated the condition in question. Whether we call it plantar fasciitis or something else--

MS. MARLOW: We have no objection.

DR. PFEFFER: My last question, very brief; in a warning, in the information that we received, on Page 55, it states, it is 3.12.3 warnings; "ESW treatment with the OssaTron should be performed with experience in the care of patients with foot and ankle disorders." Will that include primary-care doctors, and how are those types of physicians defined?

MS. MARLOW: That is a difficult issue for us. Our intent is to target orthopedic surgeons. We believe that this device is best used in the hands of orthopedic surgeons. The way that our training program is set up and the way that our business practices are right now, that is initially what definitely will happen.

I can foresee the same scenario that you foresee. I think that if there is a primary-care physician, if I may use the example of one of our clinical-study sites, at our Birmingham site. There are primary-care physicians that work with the orthopedic physicians there who would be appropriate--there would be no problem with training them along with their orthopedic colleagues to use the device.

Outside of that example, I can't say that I know what we would do. I know that we plan to hold the training course for everyone. We intend to implement it the same for everyone and, hopefully, that will adjust the situation.

DR. PFEFFER: Good. Thank you very much. It is very difficult to study plantar fasciitis because of patient compliance and follow-up issues which we have discussed. I would congratulate you on a fine effort.

DR. BOYAN: Dr. Silkaitis?

DR. SILKAITIS: Thank you, Dr. Boyan. In an effort to save time, et cetera, et cetera, many of the comments and statements that were made were very appropriate. So, therefore, I don't have anything to add. Other than we all recognize that training is important. It is not necessarily the title of the person who is either doing the training or is receiving the training, but that training is important and somehow that that is documented.

That's all.

DR. BOYAN: Thank you.

We have actually lost our consumer rep, so, while we are waiting for her to come back, why don't we go over to Dr.Aboulafia. You had some questions?

DR. ABOULAFIA: I did have just a few questions. First of all, it is not clear how long the patients remain blinded in the--specifically, if you look at all the data, the nonrandomized group dramatically was better than anybody. The best group is the outpatient; here is what we are going to do, and go ahead and do it.

While you get great results that way, our job is to look at efficacy. So we have to look at that nonrandomized treatment group differently. So there is clearly a marked placebo effect that we can all agree on, that there is at least a marked placebo effect because the sham group also improves pretty dramatically.

Were the patients who filled out their 12-week follow up still blinded to what the treatment was?

MS. MARLOW: Yes.

DR. ABOULAFIA: How do you blind them? If one group has the liquid, the bag of saline, presumably, between them, are they able to see that there is something between them and the electrode?

DR. OGDEN: No. Every patient had a blind put up between them and the treatment device. The only thing that

they were able to sense was the machine going off each time. You raised a very interesting question that I brought up and that is the patients who received treatment did not know whether they received treatment.

So, in essence, they were a pseudoplacebo patient in that they were as unaware of whether they had received the treatment as the patient that didn't. That may, indeed, have affected their perception of pain. They may have thought that, "Because I am not getting better right away, I didn't receive it," and that may have affected the way they answered some of the subjective questions. There is just no question.

I think that is probably a big explanation for the difference between those who received the treatment, not knowing what they got for three months and those who absolutely knew as a training patient they were getting the treatment.

DR. ABOULAFIA: Thanks.

DR. OGDEN: You're welcome.

DR. ABOULAFIA: The other thing is, and I know it is tough to control for these things, but there is probably a huge difference--in your inclusion criteria, you spell out that they had to have undergone certain nonoperative, not necessarily conservative, but nonoperative treatment modalities.

There is probably a big difference, though, in giving someone a week's worth of a nonsteroidal antiinflammatory versus a trial of, let's say, four weeks of a nonsteroidal antiinflammatory. There is no quantification, at least that I could get from this, of the duration of nonoperative treatment other than that they were treated for six months.

But one group was given, let's say, an orthotic and it didn't work for 5.9 months and the next time the patient was seen, he got a nonsteroidal antiinflammatory medication for three days, that might not be an appropriate inclusion criteria. Does that make sense? Any response on how that could--in other words, I think we, as treating physicians, inherently know what a reasonable nonoperative treatment prescription is. It is not clear to me that each one of those patients fit into that category.

MS. MARLOW: I think that is one of the best reasons for doing a randomized trial, because you do have--especially in a situation like ours where there are so many factors, subjective and objective, that impact a patient's perception of pain.

I think that the best answer to that is, hopefully, because we did do a well-run study, that has been controlled for by having a placebo control.

DR. OGDEN: Again, that is a very valid point to

try to determine and make as cohesive a patient population to do the studies on. We had a minimum of three kinds of treatments, and, on an average, I think it was closer to five different kinds of treatments that patients had.

Hopefully, by having that number of treatments prior to doing this, you kind of mellow out the variation in the days that the patient may have taken NSAIDs. The patients who had the orthotic devices were allowed to continue to use those, so we did not stop that, which may have introduced another variable.

DR. ABOULAFIA: Okay, great. I don't consider myself a cynical person, but let me give sort of a cynical interpretation of the data and see if you all agree or not, again recognizing this is a difficult problem to treat and you are looking at a group of patients who have already failed, for lack of a better term, on nonoperative treatment.

But what you can tell patients who are undergoing this study that--Dr. Alvarez said that people were getting back to work better, they were doing more, after his initial five patients who were the nonrandomized group who had a markedly impressively different response than the patients who were in the randomized group.

Looking at the data, I think what you can tell people is that if an investigator examines your foot, we are

going to have statistically significantly different results with this treatment than without and that you will have statistically significantly different results in terms of your own assessment of pain on walking early in the morning, but that you will not have any statistically significant difference in activity level or any statistically significant difference in terms of medication use.

Is that true or false?

DR. DeMUTH: I guess I sort of want to answer that in terms of what we were powered to show and--

DR. BOYAN: Before you start, state your name.

DR. DeMUTH: George DeMuth. I am a consultant for HealthTronics. I agree, those are the statistically significant endpoints. Actually, pain on walking is marginal and the composite is significant. But I think there is not much more you can say.

These other ones, it looks like there is a trend, but we just don't have sample size or significance to say anything about this.

DR. BOYAN: One more person has an opportunity to ask any questions she might like to ask.

Dr. Butcher, are there any questions you would like to ask either the FDA or the presenters?

MS. BUTCHER: Thank you. As the consumer rep, I have paid a little bit more attention to the labeling as

opposed to the actual things that you have already been questioned on, so I will go directly to that.

My first question is I see that comments have already been made about labeling. There are a couple of pages requesting and asking that other things be done. My question is have they been done.

MS. MARLOW: FDA has communicated those to us.

MS. BUTCHER: Yes; they have.

MS. MARLOW: As part of the requirements to develop final labeling based on your recommendations here today, we have absolutely no problem with finalizing those with FDA.

MS. BUTCHER: Okay. Well, I just have a couple of comments about the draft and, not to add anything to what they have already said, but as a consumer, it would appear to me that, perhaps, if you discuss the target patients that you were seeking to address in the first place, in the first instance, that it would give them some relief to know that, "Hey; I am not alone. I need to be in this group of people that have had difficulty with this. It is not like this is the first time we have tried to address this issue." It would give them some degree of comfort in saying, "Let me read on and get more information."

The suggestions that were made were valid. I think that, basically, the draft is good. Go for it. I

don't have any other questions for you.

DR. BOYAN: Are there any other questions from the panel? Seeing none, I would like to invite the FDA forward to read their questions, effectively their charge to us.

Panel Questions

MR. OGDEN: My name is Neil Ogden. I work with the FDA in the General Surgery Devices Branch. The first question we have to the panel; "Although the total number of complications of any type in both the active and control groups were similar, there were some types of complications observed in the active-treatment group that were not observed in the control group. These events included neural injury and irritation, plantar fascial rupture, ecchymoses if the dorsum of the toes. Does this PMA safety profile for the OssaTron treatment compare to the control treatment adequately demonstrate the absence of unreasonable risk of injury?"

DR. BOYAN: Go to No. 2.

MR. OGDEN: Question No. 2: "Do the data in this PMA demonstrate that there is a reasonable assurance that, in a significant portion of the target population, the use of the OssaTron for its intended use and the conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results?

Question No. 3: "The sponsor proposes an indication of 'The OssaTron is indicated for the use of ESW treatment of chronic heel-pain syndrome in patients who have had symptoms for a minimum of six months and who have failed to respond to conservative treatment.'

"Although the term 'heel-pain syndrome' includes the plantar fasciitis diagnosis, it may also be confused with other etiologies like stress fracture of the calcaneus, Achilles tendinitis and tarsal-tunnel syndrome. Please comment on the patient population for which this device should be indicated."

Thank you.

DR. BOYAN: Thank you.

If the person who is handling the slide could go back to Panel Question 1, please. We will leave the question up so everybody can see it while we are discussing. I would like to see if anybody on the panel would like to come forward with an answer to this question and why don't we go--Dr. Pfeffer, would you like to begin the comments?

DR. PFEFFER: I read this information in detail prior to our meeting and I do not consider these complications consequential to affect approval of this device one way or another.

DR. BOYAN: Why don't we come this direction. As each panel member has an opportunity to address this, they

don't need to repeat a statement that has already been made. If they agree or disagree, that is all they need to say, or if they have something that they would like to add to the information, add this information at this time.

Dr. Wright.

DR. WRIGHT: I agree.

DR. CHENG: I agree.

DR. YASZEMSKI: I will note that I think Dr. Ogden addressed these already and there are no issues remaining related to them.

DR. BOYAN: Dr. Finnegan? Oh; she left us. Dr. Larntz?

DR. LARNTZ: I have no opinion.

DR. LEWIN: I don't have any comments.

DR. ROBINSON: Agree.

DR. BOYAN: Dr. Goldman; are you reading the question?

DR. GOLDMAN: I know my answer. I think that the assessment of nerve injury probably was not adequate to make a determination, in my opinion.

DR. ABOULAFIA: I agree with Dr. Yaszemski.

DR. BOYAN: Dr. Silkaitis, do you have a comment you would like to make?

DR. SILKAITIS: No comment.

DR. BOYAN: And none for you, either?

MS. BUTCHER: No comment.

DR. BOYAN: Dr. Witten, have we addressed this sufficiently to the usefulness of the FDA?

DR. WITTEN: Yes; thank you.

DR. BOYAN: Okay. Let's go to Panel Question No. 2. Dr. Robinson, would you like to tackle this question first?

DR. ROBINSON: The question that reasonable assurance in a significant portion of the target population, its intended use and conditions; my short answer would be yes, and it will provide some clinically significant results.

DR. BOYAN: Is there anybody on the panel that would like to make a further comment on this question? Dr. Larntz?

DR. LARNTZ: I am not sure if I understand the question totally so what I will say is I think this device will give, has been proven to give, short-term pain relief for a proportion of the individuals probably on the order of less than 50 percent or around 50 percent of the population.

As long as we understand that we are getting short-term pain relief, that is the result of using this, and no indication of duration of relief has been proven and, in fact, no indication that it is a large proportion. It is at least 15 percent, maybe is up to 50 percent, and gives

some pain relief. That is what I would say we know about this.

DR. BOYAN: Dr. Aboulafia?

DR. ABOULAFIA: I would ask the same question again. I hate to come across as the cynic, especially in someone who doesn't routinely treat plantar fasciitis. So I will certainly defer to Dr. Pfeffer and especially Dr. Ogden as well to answer.

Convince me that this is a reasonable treatment if the goal of chronic heel pain is long-term lasting results. It seems to me that the effects are statistically significant in one out of four parameters that were used as criteria to evaluate the efficacy of the device at 12 weeks, and that we have no data on anything to suggest that it does provide long-term durable results and that even the 12-week results showed that your heel hurts less if a doctor presses on it, but you still take pain medication and your activity level is unchanged.

Am I looking at this cynically? I don't intend to. Dr. Pfeffer, or Dr. Ogden?

DR. BOYAN: Actually, they are off line now, but we will give them an opportunity to respond back. They get one more chance. Dr. Pfeffer?

DR. PFEFFER: The data speaks for itself. We have all seen it. The only clinical comment I can make is that

the study in a group of patients like this longer than 8 weeks or 12 weeks is, perhaps, almost impossible. It is just not a group that stays together and is easy to follow.

So your data interpretation, I would certainly agree with. To say that our charge to the company would be to go back to study this for six months or one-year follow up, I think would be almost undoable.

DR. ABOULAFIA: Let me ask why. We do this with county gunshot-wound patients which I think is a much tougher population, frankly. We do it with intravenous drug abusers with at least 50 percent follow up which I think is a tougher population. So that is item No. 1, the follow up beyond 12 weeks.

But I will even ask the question about has industry shown that it is an effective device for 12-week follow up? There are two parts of this. At 12 weeks, can we, as a group, say--I agree that it is a safe device. Can we say that, at 12 weeks, it is effective since there were four parameters tested and one out of four maybe shows a significant difference.

DR. PFEFFER: I have no new comment about the first point. Just the second point is that if someone has a gunshot or someone has a cancer or some serious injury, they are much more likely to stick around their doctor than someone who has had two years of heel pain that has a

certain amount of intervention and then may have some decrease in their heel pain.

It is a group that is just hard to follow. This is a relatively minor problem, at least in my own personal experience. I think a 6-month study or a year study would be wonderful, but I think it would be very, very hard to do.

DR. ABOULAFIA: Except we are selecting for a group of patients who have proven six months of follow up so far, and we are selecting for a group of patients who admit that they have a significant problem because their VAS is 5.0 or greater. So I would say, if anything, we are selecting for a group of reliable patients who have proven that they are willing to at least stay with the physician under care and treatment--not maybe one physician, but a physician, for at least a six-month interval.

Then there is the third selection, the physicians, themselves, who have not been involved in clinical trials. If a patient doesn't seem like they are going to be able to participate, like they are planning on moving out of town, we don't include them.

DR. BOYAN: I think, to summarize this discussion, we are all in agreement that the 12-week data is adequate. When we get to the final voting and recommendations and comments that we might want to convey to FDA, we certainly are clear, also, that we don't have more long-term data to

rely on. So that will come out at that time, I think, pretty adequately.

Dr. Cheng, did you have something that you would like to add that is different?

DR. CHENG: I was going to add that I am wondering if your concern--statistically, what Kinley said is correct. However, clinically, it may not be that much of a problem. My understanding of this disease is that, once people are better, the likelihood of relapse is pretty low. I defer to my colleagues if I am wrong, but that is my understanding.

DR. BOYAN: Thank you for your comment. Is there any other comment that is directly related to Question No. 2? I look around the room. Seeing none, Dr. Pfeffer, if you would like to take a first stab at this one, it would be great.

DR. PFEFFER: The separation of these diagnoses clinically is very straightforward. The diagnosis of heel-pain syndrome, if you will, or plantar fasciitis is made easily by maximal focal pain over the medial calcaneal tuberosity that may extend for a centimeter or two distally along the course of the plantar fascia.

The most specific, and also well-recognized by the public, diagnosis for this condition is plantar fasciitis or, specifically, proximal plantar fasciitis. That is the term I would recommend be used. It is quite distinct from

any of these other diagnoses. That is population that, in fact, was examined by this study.

DR. BOYAN: Thank you. Let's just take a quick opportunity to see if anybody else would like to comment on Question No. 3.

Seeing none, we are doing very well here. Let me tell you that we are doing better than anticipated, so I have to make it--oh, yes; I have to ask Dr. Witten.

Dr. Witten, did we answer Questions 2 and 3 adequately for the FDA?

DR. WITTEN: Yes; thank you.

DR. BOYAN: Now, this is the deal. It is about 12:20. I don't want to rush the vote or the discussion after the vote. So I will ask the company one thing. When we come back, after we have lunch, you will be given an opportunity to address anything that you feel you need to clarify.

If you feel like you are ready to do that now, I would welcome you to do that. Then, if something comes up in your discussions with each other over lunch that is ground-breaking that you need to bring up, you can.

MS. MARLOW: I appreciate that. I think the only thing I would like to do is try to clarify this issue of long-term follow up. I think we got a little bit derailed on that issue.

Let me try to explain how we constructed the study protocol. Patients had to stay in the study until 12 weeks. When they signed their consent, they were asked to, "Bear with us, don't go after any other form of treatment, come back for follow up. If you are a failure at 12 weeks, we recognize you are going to want to try to do something else for your heel pain and you may be released from the study at that point in time."

At that time, after that 12-week follow-up visit, if the patient says, "Yes; I want to go do something else. I am still having pain. I am unhappy," we said, "Great. Go. But we are going to tell you your options." And then, at that point in time, they were told that they were eligible for a retreatment.

Therefore, the patients that did not opt for retreatment could go and have another treatment. There was no point in us following those patients thereafter because we would be studying some other treatment for heel pain. So it is mandatory that the successes were followed. It was voluntary for the failures who did not have other treatments to be followed. We continue to follow those patients.

We have an open IDE. We are complying with the requirements of that IDE. The 25 or 26 patients you referred to Dr. Larntz, that were not recorded in the PMA, were not recorded merely because they had not yet reached

twelve weeks.

We have data for those patients now. We have data for all the patients we continue to follow. I appreciate Dr. Pfeffer's defense of how difficult this patient population is and I will agree. This is a very difficult patient population to follow, but we are continuing to follow them.

Our lost-to-follow-up rate is only slightly higher than I reported for the subset of patients that were lost before the 12-week follow up. They are not lost. They are just recorded--

DR. LARNTZ: Can I ask, just to make sure I clarify? You are saying that 119 patients, they are the only patients that were eligible for a 12-week follow up, not 130.

MS. MARLOW: That's correct.

DR. LARNTZ: Okay; I didn't get that.

MS. MARLOW: The rest of those patients, we are still following. As a matter of fact, we have enrolled a few more.

DR. LARNTZ: Okay; I apologize for that.

MS. MARLOW: That's okay. It is absolutely no problem.

DR. LARNTZ: With respect to duration, I was only worried about the successes.

MS. MARLOW: Right; I understand.

DR. LARNTZ: In the successes, or 40 percent of the successes didn't come back at six months.

MS. MARLOW: Actually, that is the same story. They were just not eligible. They are out to six months now. We have the data. We had to look at the data briefly to let FDA know whether there were any changes. There is a requirement in the regulations that say threes months before the PMA--or three months after the PMA, excuse me--"Do you have anything new to disclose?"

We had the statistician take a quick look. He said, "No; there is nothing new here." So we went about our business. There is nothing new to disclose. What we have taken a look at for the patients we have continued to follow is nothing different than what we have presented here today.

When FDA gets the final report on the IDE, that is exactly what will be in there.

DR. LARNTZ: But you didn't report how many were eligible at six months. You are saying everyone who was eligible at six months was reported? They all came back?

MS. MARLOW: Anyone who was eligible was reported; yes.

DR. LARNTZ: When you say "follow up, yes/no," I apologize. I will stop. I am slowing down the process. If it is true, then it certainly is a problem with my reading

of your report. And I apologize.

MS. MARLOW: It's okay. I'm sorry, but I do want to try to get this cleared up. The other point I would like to make is we tried very hard not to make any claims about duration of results. The reason for that is even if we had follow up on 500 patients, I can't give you any assurance that it is because of the OssaTron treatment.

The natural history of the condition is that people are going to get better. It may take them five years. It may take them ten years. But most of them eventually get better.

So, even if I had those data to give you, it would probably still be controversial as to whether the continued improvement is the natural history, treatment effect. But we know that, at 12 weeks, it is probably treatment.

DR. BOYAN: Thank you very much.

We will break for lunch now. Before you get up, we are going to only take a 30-minute lunch. I want to remind everybody that this is a confidential proceeding, and especially remind the panel that we will not be discussing anything that has gone on here this morning, during lunch, so, as we leave the room, this is a--oh; all right.

I must clarify that. I am reminded, this is an open session. We want to remind the panel not to discuss the topic while we are at lunch. Now, all the panel will go

at

down to the restaurant and we will reconvene here in 30 minutes.

[Whereupon, at 12:30 p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

A F T E R N O O N S E S S I O N

[1:12 p.m.]

DR. BOYAN: Right before we broke for lunch, the company was in the process of making their final comments. They have now had 35 minutes to think over their pain. Is there any last thing you would like to say? No? The answer is no.

So we can now move on to the next part of the meeting. We have one brief bit of business. We have to have a second open meeting where the people are invited to address the panel, and it is now until all those people have had an opportunity to speak.

Open Public Hearing

DR. BOYAN: We will now proceed with the open public session of this meeting. I would ask, at this time, that all person addressing the panel come forward and speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public session of the meeting disclose which company they represent and whether they have financial interest in any medical-device company before making your presentation to the panel. In addition to stating your name and affiliation, please state the name of

your financial interest if any.

Is there anybody in the public who is wishing to address the panel? Seeing none, and I have already asked HealthTronics if they had any final comments before the panel proceeds, and they have none. So we will go on to the voting.

Vote

DR. BOYAN: I would like to now ask Mr. Hany Demian to read the voting instructions for the panel.

MR. DEMIAN: I will now provide you with the panel recommendation options for premarket approval applications. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical-device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits and the recommendations must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under the conditions of use outweigh any probable risks.

Effectiveness is defined as reasonable assurance

that, in a significant proportion of the population, the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows: one, approval. There are no conditions. Two; approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions such as a resolution of clearly identified deficiencies which have been cited by you, the panel, or FDA staff.

All the conditions are discussed by the panel and listed by the panel chair and then voted on one at a time. For example, you may specify what type of follow-up information the panel or FDA should evaluate prior to or after approval. Panel follow up is usually done through homework assignments to one or two primary panel reviewers of the application or to other specified members of this panel. Formal discussion of the application at future panel meetings is usually not held.

If you recommend postapproval requirements to be imposed as a condition of approval, then your recommendation should address the following points; the purpose of the requirement, the number of subjects to be evaluated, and the types of reports that should be submitted.

The third option is not approvable. Of the five reasons the Act specifies for denial of approval the

following three reasons are applicable to your panel deliberations: the data do not provide reasonable assurance that the device is safe under the conditions that are prescribed, recommended or suggested in the proposed labeling; reasonable assurance has not been given that the device is effective under the conditions that are prescribed, recommended or suggested in labeling; and, based on a fair evaluation of all material facts in your discussions, you believe the proposed labeling to be false and misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in approvable form.

Traditionally, the consumer representative and the industry representative do not vote. Dr. Boyan, as panel chair, would only vote in the case of a tie.

Dr. Boyan?

DR. BOYAN: Before beginning the voting process, I would like to mention, for both the panel's benefit and for the record, that the votes taken are votes in favor of or against the motion made by the panel. Votes are not for or against the product.

Dr. Robinson, are you prepared to make a motion?

DR. ROBINSON: Yes; I am. I would make a motion

to approve this with no conditions. My rationale for that would be briefly that this is an extremely debilitating disease in some patients. It is extremely frustrating for both patients and physicians in a significant number of instances.

Although the group effect was moderate, the individual effect was marked in some individuals. Thus, I think this offers us a new choice for treatment in a frustrating disease.

DR. BOYAN: We will have a chance for discussion here in a second. Is there a second for the motion?

DR. YASZEMSKI: Second.

DR. BOYAN: Yaszemski seconds. Is there any discussion of the motion? Dr. Robinson, do you want to finish your discussion?

DR. ROBINSON: I was just going to address there are no safety concerns for me and there are only minor issues concerning labeling that I think can be worked out between the sponsor and FDA.

DR. BOYAN: Any other comments? Dr. Finnegan?

DR. FINNEGAN: Actually, I think there are some safety concerns. I think that particularly neurologic injury and also the use of the device in certain hands. So I actually cannot support that vote.

DR. BOYAN: Any other comments before we vote on

the motion?

All those in favor of voting for approval without conditions, please raise your hand.

[Show of hands.]

I count five votes for approval without conditions--six? Raise your hand again.

[Show of hands.]

Six votes for approval without conditions. All those against approval without conditions, raise your hands.

[Show of hands.]

I count three votes--four votes. Why am I having trouble counting. You are asking a question? Yes?

DR. PFEFFER: Could you outline the types of conditions that might be added?

DR. BOYAN: No.

DR. PFEFFER: We are just voting on this.

DR. BOYAN: That comes next. So you are voting which way? Against approval without conditions?

DR. PFEFFER: For there being some conditions.

DR. BOYAN: You would like there to be conditions, so you are voting against this motion. So there are four votes against approval without conditions.

Are there any abstentions?

[No response.]

Let me remind you, the motion carries. I just

want to remind everybody here, again, that this is a vote for the motion and not for the product. The FDA hears absolutely 100 percent of everything we say, and they will take all of this information back and they will make the final determination, not us.

So I think that ends this discussion; right?

DR. WITTEN: We need to go around the room.

DR. BOYAN: That's right. I forgot the very special part. This is the part that they really listen to so here is where you get to do your thing. We will go around the room, one at a time, and everybody gets to explain why they voted the way that they did.

DR. WITTEN: And state your vote, too.

DR. BOYAN: And state your vote out loud for the record. Dr. Aboulafia, would you start, please.

DR. ABOULAFIA: I think everyone knows what I am going to say because I already said it, so I will just outline it very briefly. I am not concerned about safety issues. I think all those things have been appropriately addressed. I would add that I thought it was a well-designed study and the integrity of the data is not in question at all.

I thought labeling concerns were well addressed. I think the question that was raised about who can use it and who can't use it is an impossible question to answer. I

am licensed to administer general anesthesia. I would never do it. You can't label a device for one doctor to use and not another if they are a licensed, practicing physician. So that was not a concern for me.

The only concern I had was whether the data supports that it is an effective product. I have said that before and there is no point repeating it.

DR. BOYAN: Dr. Goldman?

DR. GOLDMAN: Although I raised some issues regarding the process of the data collection, I think that it was a well-done study. I also think that it also was effective at the time point with the primary endpoint. Although there are trends, it is not clear that it has long-term effects, although it probably does.

My concern, and I did approve this without conditions, is that in the labeling, which would be, I guess, minor issues to clarify the labeling, is that it should include precautions for people that are smokers, that may have microvascular disease, people with diabetes who might have both microvascular disease and peripheral neuropathy, and anyone else who might have a peripheral neuropathy such as people with a long history of alcohol use.

So my concerns only involve labeling.

DR. WITTEN: Could you just state whether you

voted for the motion or against it?

DR. BOYAN: He did. He was for.

DR. WITTEN: Thank you.

DR. ROBINSON: I voted for approval without conditions and then blurted out my rationale before I should have. My minor concerns are exactly what Dr. Goldman is mentioning plus the fact I think the FDA and sponsor need to talk about just assurance of an adequate training program.

DR. LEWIN: I voted for approval without conditions. As I mentioned before, I primarily looked into the technical specs and I was very impressed with the solid and very complete documentation which the company provided. They definitely know what they are doing

The company strongly supports training of the MDs or whoever will be performing the treatment. The device offers pain relief when all other treatments fail to do this. Overall, I haven't seen any serious contraindication. So I am convinced that they will do a good job.

DR. LARNTZ: I voted against approval without conditions. I would have voted for approval with - conditions. The conditions would have involved finishing the duration analysis and making sure that no danger or problem came in long-term use of the product.

DR. FINNEGAN: I voted against the approval without conditions. I would have voted for approval with

conditions. My concerns are several. There is a long history of instruments getting into the hands of people who have not been properly trained and this actually usually comes back to haunt everyone involved in the instrument.

I think mandatory training is essential. Also, I think that there is enough data from gunshot wounds, in particular, to show that shock-wave injury to nerves is a problem. Around the foot, either loss of sensation or motor function causing deformities is a significant problem and I think there should probably be some postmarket surveillance on this.

DR. YASZEMSKI: I voted for approval and I have nothing to add to what has already been said.

DR. CHENG: This is Cheng. I voted for approval without conditions. My only concern is dealing with inappropriate usage for, perhaps, acute disease or I think every practitioner who takes care of foot problems, M.D. or otherwise, will use this as reimbursement issues will drive them to use it more frequently. But I think that is difficult to enforce through any type of condition-or, perhaps, outside the FDA purview.

DR. WRIGHT: I voted for approval.

DR. BOYAN: Do you want to add any other comments?

DR. PFEFFER: Glenn Pfeffer. I voted against the blanket approval. I certainly would have supported this

with conditions. The conditions that I would have are, perhaps, out of the purview, however, of this panel and the FDA. The conditions I would like to see is that everyone who uses this device has an appropriate training course and that the device not be used for the treatment of plantar fasciitis or heel-pain syndrome in a patient who has symptoms for less than six months.

Otherwise, I completely support this product.

DR. BOYAN: Although you didn't vote, is there any comment that you would like to make, Dr. Silkaitis?

DR. SILKAITIS: No. I have no comment.

DR. BOYAN: Any comment?

MS. BUTCHER: No.

DR. BOYAN: Dr. Witten, have you received enough information?

DR. WITTEN: Yes; and I would like to thank the panel and the sponsor and the FDA presenters here.

DR. BOYAN: Okay; so this part of the panel meeting is now--let me just make sure I am covering the territory here. Ah; I have to state it over.

The panel is recommending that the premarket approval application for HealthTronics OssaTron be approved without conditions.

I now bring this meeting to an end.

DR. WITTEN: This portion. We have another

product.

DR. BOYAN: Well, yes; I know. But HealthTronics is freed from captivity. It is the panel that is not free.

Open Public Hearing

DR. BOYAN: We will go ahead and open up the open public hearing. This is an open public hearing session. I would like to ask at this time that all person addressing the panel come forward and speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public session of the meeting disclose which company they represent and whether they have financial interest in any medical-device company before making your presentation to the panel. In addition to stating your name and affiliation, please state the name of your financial interest if any.

Is there anybody in the public who is wishing to address the panel?

Session 2: Howmedica Osteonics PMA P000013

DR. BOYAN: We will now proceed with the second PMA for a ceramic-on-ceramic total hip arthroplasty. This will be application P000013, Howmedica Osteonics Corporation ABC/Trident Systems. We will now consider the premarket approval application for the Howmedica Osteonics Corporation

ABC/Trident Systems.

I would like to remind public observers that, while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

We are now ready to begin with the sponsor's presentation, followed by the FDA presentation. We have several new members of the panel that we need to introduce. I think what we should do is ask the Executive Secretary, is there anything else you need to do before we start this panel?

MR. DEMIAN: Actually, do you have copies of your presentation? Do you have copies for the panel members?

MS. STAUB: We can make some but we don't currently have them, no.

DR. BOYAN: We can handle that. What I would like to do is introduce Dr. Steve Li. Steve, why don't you say who you are, where you are from and what you do?

DR. LI: Steve Li, Senior Scientist, Hospital for Special Surgery, Department of Biomechanics and Biomolecular Design, New York City.

DR. BOYAN: I am thinking, Executive Secretary, since we have a whole new company here we should probably go once more around the room and have everybody introduce themselves for the record.

MR. DEMIAN: I agree.

DR. BOYAN: So, let's start. Dr. Aboulafia?

DR. ABOULAFIA: I am still Albert Aboulafia --

[Laughter]

-- I am working at Sinai Hospital and the University of Maryland, both in Baltimore.

DR. LARNTZ: Kinley Larntz. I am a statistician. I am Professor Emeritus of Statistics at the University of Minnesota and my research interests are in clinical design and analysis of data.

DR. FINNEGAN: Maureen Finnegan, Associate Professor, U.T. Southwestern. My areas of interest are trauma and sports.

DR. YASZEMSKI: Michael Yaszemski, Departments of Orthopedics and Bioengineering, Mayo Clinic; clinical and adult reconstruction and spine surgery and research and tissue engineering.

DR. BOYAN: I am Barbara Boyan. I am Professor and Director of Orthopedic Research at the University of Texas Health Science Center at San Antonio, and my specialty is bone and cartilage biology.

DR. CHENG: My name is Edward Cheng. I am with the Department of Orthopedic Surgery at the University of Minnesota, and my interest is in reconstructive surgery, muscle cell oncology and osteonecrosis.

DR. LYONS: I am John Lyons. I am from Erie, Pennsylvania. I am a private practice orthopedist. Adult reconstruction is my area of interest and I am also a biomedical engineer.

DR. SILKAITIS: My name is Raymond Silkaitis. I am the industry rep., a non-voting member of the panel. I have a Ph.D. in pharmacology and I am a registered pharmacist.

MS. BUTCHER: My name is Vicky Butcher. I am -- what am I? I am the consumer rep., also a non-voting member. My background is in teaching the law, and I have served as the consumer consortium member for the FDA.

DR. BOYAN: Thank you. If I have already read this, that is how it is! I would like to remind public observers that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

We are now ready to begin with the sponsor's presentation, followed by the FDA presentation. I would like to ask that each speaker state his or her name and affiliation to the firm before beginning the presentation.

The sponsor's presentation will include an introduction by Beth Staub and Michael Manley; product description by Thomas McCarthy; laboratory testing by Michael Bushelow; implantation technique by James D'Antonio;

clinical data by Michael Manley and, finally, summary and conclusions again by Michael Manley.

Sponsor Presentation

Introduction

MS. STAUB: Good afternoon.

[Slide]

My name is Beth Staub, and I am the vice president of quality assurance, regulatory affairs and clinical research for the Howmedica Osteonics Corp.

[Slide]

On behalf of Howmedica Osteonics, we are all pleased to be here this afternoon to present safety and efficacy data that we have collected demonstrating the safety and efficacy of two alumina on alumina ceramic bearing surfaces, ABC and Trident.

Since their introduction in the '70s, the wear resistance and biocompatibility of ceramic couplings has been widely reported, and significant improvements have been made to materials and manufacturing processes. The ABC and Trident Systems incorporate these improvements, as well as design elements that are important in ceramic/ceramic total hip arthroplasty.

[Slide]

In 1996, the Osteonics Corporation initiated a prospective, controlled, randomized multi-center trial to

collect clinical data on the ABC alumina bearing system. This study included two styles of acetabular shells, an HA, or hydroxyapatite-coated femoral stem, and a polyethylene control group.

[Slide]

In 1999, Howmedica Osteonics obtained FDA approval to begin a supplement to the original ABC study, evaluating the Trident bearing design. The trident bearing differs from the ABC in its locking mechanism. This enhanced locking mechanism affords the surgeons more revision options, and helps protect the ceramic component from chipping during insertion. The surgeons with the greatest number of implants in the original ABC study were selected for the Trident arm, and the same polyethylene control group was used.

[Slide]

This table provides an overview of the components used in the study. All are commercially available by the 510(k) process with the exception of the two we are asking the panel to recommend for approval today, the ABC and Trident alumina inserts.

ABC System I used a microstructured or porous coated shell, the ABC alumina insert with the aluminum head and the HA hip stem. The ABC System II shell featured a Secur-Fit coating, titanium Arc-Deposited with an HA-coated

surface. All other components in System II are identical to those in System I.

The Trident arm of the study was similar to the ABC System II, using an Arc-Deposited HA-coated shell but substituting the Trident locking mechanism on the acetabular components.

The control group for both the ABE and Trident arms received a microstructured shell, along with the standard polyethylene liner and cobalt chrome femoral head.

[Slide]

Today we will be presenting a summary of our clinical and non-clinical data. Dr. Michael Manley, Howmedica Osteonics chef scientific advisor, will moderate our program, and I will now turn the agenda over to Mike.

Introduction

DR. MANLEY: Good afternoon. I am Michael Manley, chief scientific advisor for Howmedica Osteonics.

This presentation is in five parts. First, we will discuss the specific design of the devices used; secondly, the lab testing that was done on those devices; thirdly, the implantation technique for the devices; fourth, a summary of the clinical data, and, finally, within the discussion we will address the questions raised by FDA.

[Slide]

To describe the design of the devices used, let me

call on Tom McCarthy, project engineer of the acetabular team at Howmedica Osteonics. Tom?

Product Description

MR. MCCARTHY: Thank you, Mike. I would like to take the next few minutes to describe the designs of the implants associated with this study.

[Slide]

We call the ceramic-on-ceramic design the ABC System. ABC is an acronym that stands for alumina bearing couple. The study consisted of three separate systems referred to as Systems I, II and III.

Systems I and II had ceramic bearing surfaces, while System III, the study control, had a polyethylene bearing surface. All implant combinations in this study used the same femoral stem, an Osteonics Omnifit HA-coated stem. And, all acetabular shells had the option of using the same screws.

[Slide]

I will start out by describing the study control. It consisted of an Osteonics PSL microstructured titanium shell with porous coated beads, a polyethylene liner, and a cobalt chrome femoral head. Only neutral poly liners gamma irradiated in an inert atmosphere were used.

[Slide]

System I consisted of an ABC PSL microstructured

titanium shell with porous coated beads, an alumina acetabular insert, and an alumina femoral head.

I want to note that the ceramic inserts are the only components under IDE investigations in this study as all other components have been 510(k) cleared.

[Slide]

In System II, an ABC Secur-Fit Arc-Deposited coated titanium shell with HA was used. The alumina femoral head and insert bearing combination is the same as in System I.

[Slide]

A unique feature with the ABC shells is the ceramic protection rim. The lip of the shell extends beyond the surface of the ceramic insert in order to protect the ceramic insert from neck impingement and possible damage.

[Slide]

A cementable poly liner was also offered as a revision option for Systems I and II which used the ceramic insert. It is cemented directly into the shell.

[Slide]

The study arm-used ceramic components from the Trident System. The design goal of Trident was to enhance the ABC System with design advantages beyond the ceramic insert.

The Trident System design allows for ease of ceramic liner insertion, intraoperative flexibility; and

more revision options. The shell allows for independent locking of ceramic and poly inserts, both of which can be chosen intraoperatively or at time of revision.

[Slide]

The Trident study arm, again, used the same femoral stem, ceramic heads, and screws as with ABC. In addition, a 36 mm femoral head was used. The shell was an Arc-Deposited coated titanium shell with HA. The shell outside geometry and coating were identical to that of the ABC System II. The ceramic insert has a permanently assembled titanium sleeve on the outside with the same ceramic insert protection rim feature.

[Slide]

On the left you see a cross-section of an ABC cup, and on the right, a Trident cup. The metal sleeve has a taper to taper fit within the shell, as is shown right there. We were able to add a metal sleeve essentially without decreasing the thickness of the ceramic insert. The most important features remain the same. Both ABC and Trident have identical bearing surface dimensions and tolerances for both the ceramic head and the inserts; identical range of motion and ceramic protection rim; and identical shell contact with the bone. Thank you.

[Slide]

DR. MANLEY: Michael Manley again. Thank you,

Tom. I would now like to introduce Michael Bushelow, who is assistant director of device evaluation at Howmedica Osteonics, who will discuss the laboratory testing behind these devices. Mike?

Laboratory Testing

MR. BUSHELOW: Thank you, Mike.

[Slide]

I will be spending a few minutes describing some of the mechanical testing and analyses that were preformed to ensure safety of both the ABC and Trident acetabular cup systems.

Specifically, I will describe the strength testing that was performed on both system designs based upon ISO, ASTM and FDA procedures and guidelines, as well as the finite element analysis that was performed to look at bone stresses at the fixation interfaces.

[Slide]

Presently, there are no standard test methods for evaluation of ceramic inserts used in acetabular cups. Therefore, standard test methods for evaluation of ceramic femoral heads were modified and used for these evaluations.

The test methods used include ultimate compression strength testing, axial fatigue strength testing, and post-fatigue ultimate compression strength testing.

The figure on the slide shows the general test

set-up used for all three test methods. The methods are based upon ISO standard 7206-5 and the present ASTM draft standard for evaluation of ceramic femoral heads.

Based upon the FDA guidance document for ceramic femoral heads, the performance requirements for the ceramic inserts were established. Inserts must have an average ultimate compression strength value of 46 kN with no single insert having a strength lower than 20 kN. Inserts must survive 10 million cycles of fatigue at loads between 1.4 and 14 kN. Finally, inserts that have been axially fatigued must have UCS values greater than 20 kN.

[Slide]

This slide shows the results of the ultimate compression strength testing. Please note that the ABC System is available in only 28 mm and 32 mm sizes, while the Trident has an additional 36 mm size insert.

The recommended FDA guidance performance standard is indicated by the yellow line on the graph. It can be seen that all components exceed this standard with average strength values ranging from approximately 56 kN to 67 kN. It should be noted that in all cases individual inserts had strengths greater than 43 kN.

[Slide]

This slide shows the results of the axial fatigue testing and the post-fatigue ultimate compression strength

testing. All had survived 10 million cycles without failure at the 1.4 kN to 14 kN load range.

The recommended FDA guidance performance standard for the post-fatigue ultimate compression strength testing is indicated by the orange line on the graph. Results show that the inserts post-fatigue ultimate compression strength significantly exceed the performance standard, yielding average strength values ranging between 52 kN and 62 kN.

[Slide]

This slide summarizes the data from the previous two slides, showing all of the pre- and post-fatigue UCS data for the 32 mm size inserts. This graph shows that the ultimate compression strength for both the ABC and Trident inserts is minimally, if at all, affected by the fatigue loading. Note that minimal differences are shown when comparing pre- and post-fatigue ultimate compression strength values.

Secondly, it should be noted that all testing, both pre- and post-fatigue showed average ultimate compression strength values that exceeded the 46 kN limit, with no single head showing a value less than 20 kN. In other words, all tested inserts from both the ABC and Trident Systems exceeded the FDA guidance document pre-fatigue performance criteria.

[Slide]

Finally, this graph is shown to put some perspective on the performance standards used to evaluate these ceramic inserts. Showed in red and yellow are performance standards presently used when evaluating other components within the total hip system. ISO 7206-8 is the accepted performance standard, 2300 N, for the body region of a total hip arthroplasty femoral component. While no standards are available for the neck region, CeramTec has proposed a value of 4300 N, while at Howmedica Osteonics we use a minimum value of 5300 N.

The next two bars represent the FDA guidance performance standards for ceramic femoral heads, once again a fatigue strength of 14 kN and an average ultimate compression strength of 46 kN.

Finally, the last three green bars show results of the static testing of components, including the alumina femoral head used in both the ABC and Trident acetabular cup systems.

[Slide]

I am going to switch gears here and discuss analyses that were preformed to look at the fixation interfaces and compares stresses in the bone due to implantation of the ABC and Trident acetabular cups.

All analyses were performed using the ANSYS finite element software. All models were 2-dimensional

axisymmetric models and, therefore, represent full 3-dimensional geometry. The models included surface-to-surface contact elements at the bone/shell interface. The models looked at stresses in the bone due to initial press-fit of the acetabular cups.

Multiple analyses were performed to look at the effect of overall stiffness of the components and stresses at the fixation interface. Shell stiffness was analyzed as a function of shell design, ABC and Trident, and within each shell design by modifying the insert and shell materials.

The ABC and Trident inserts were evaluated with both alumina and polyethylene inserts. Additionally, analyses modeling the shells as cobalt chrome alloy were performed to look at a case where the shell is as stiff as the presently available components.

[Slide]

Shown here are the two models used for the evaluations. The upper left model shows the ABC configuration and the lower right model shows the Trident configuration. Material properties of the various components were modified to look at the effect of shell and insert material on both stress.

[Slide]

A typical maximum principal stress contour plot for the ABC and Trident cup systems are shown in this slide.

Please note that the stress patterns and magnitudes are similar for both designs. These results remained consistent for all design and material variations analyzed.

[Slide]

The bar chart shown here shows the maximum principal stress calculated for each analysis performed. Results indicate that bone stresses at the shell fixation interface are similar at both the ABC and Trident cup systems. Additionally, the insert material and shell material had little effect on the stress magnitude and distribution at the fixation interfaces.

[Slide]

In summary, variables investigated included shell design, shell material and insert material. Results indicated a maximum 5 percent difference in bone stress due to these design variables, and it can be concluded that for these cup designs overall there was minimal effect on bone stress magnitude and distribution at the fixation interfaces.

[Slide]

Presented today are results from several of the tests and analyses that were preformed to ensure the safety of both the ABC and Trident acetabular cup systems. Mechanical testing, recommended by ISO, ASTM and the FDA for ceramic heads, and performance standards recommended by the

FDA were modified and used to evaluate the alumina inserts of these two systems.

Results indicate that the inserts easily exceed the recommended parameters standards. Finally, analyses to look at the bone/shell fixation interface showed similar bone stress magnitudes and distribution when comparing between the ABC and Trident Systems. Thank you.

DR. MANLEY: Michael Manley again. Thank you, Mike.

[Slide]

Dr. James D'Antonio, an orthopedic surgeon from Sewickley, Pennsylvania, will now describe the surgical technique used with these ceramic/ceramic bearings. Dr. D'Antonio has an academic appointment to the University of Pittsburgh, and is a principal investigator in the ABC study. Jim?

Implantation Technique

DR. D'ANTONIO: Thank you, Mike. My name is James D'Antonio, and I have disclosed financial arrangements with Howmedica Osteonics, which do include some compensation for consulting services. I also own stock in the parent corporation, Stryker.

At this time, I would like to outline for you the surgical technique that is used for the implantation of both the ABC and Trident hip systems.

[Video presentation]

The preparation of the acetabulum is by standard technique using hemispherical reamers. This first case is a 38-year old active man, disabled from osteoarthritis. The hemispherical reamers prepare the acetabulum in an under-sized fashion so that when this implant is placed it will fit snugly.

This implant is from the System II, the Secur-Fit implant with an HA coating. It will now be impacted into the prepared cavity within the acetabulum, and following impaction, again, will achieve a snug, tight fit. The positioning and placement is important.

Shown now is the insertion of the ABC alumina shell. It is first softly placed within the metal liner. A finger is passed around the rim to ensure that it is fully seated before impaction. Once that is ascertained, then impaction to secure the peripheral taper lock occurs.

We then irrigate and flush and examine to make sure it is seated and if, indeed, there were any problems or defects or chips that would easily be identified by staining of the body fluids. One sees there the implantation of the shell and the alumina ceramic liner.

The femoral side is prepared with tapered reamers and broaches. It is machined in a fashion to receive this tapered titanium stem that is coated with hydroxyapatite in

the proximal third. This stem has a 13-plus year track record now, with a 99-plus percent fixation success.

The alumina ceramic femoral head is then impacted, again, to secure the taper lock. This shows the system fully implanted. This is the ABC System.

[Slide]

This is the postoperative x-ray in this individual patient.

The second case is that of a 31-year old woman, a large woman, 6 ft., 190 lbs., college basketball player who now is a high school basketball coach. She had a slipped capital epiphysis when she was a teenager and now has disabling osteoarthritis.

[Video presentation]

The acetabulum was prepared in the same fashion. The socket here has the same outside geometry and surface as the previous one that I showed you, the Secur-Fit titanium Arc-Deposited with an HA coating. It also will then be placed in a slightly under-sized hemispherical cavity to create a very tight, snug fit once it is placed and impacted into its proper orientation.

Once that is accomplished, the inside of the shell will be irrigated, cleansed, and cleared of any debris, as with the ABC System.

Here, the Trident insert, the alumina insert which

shows the metal backing as you have seen, will now be placed first by hand. One of the advantages of the Trident is that this is technically easier to do than with the ABC System. The locking tabs will be lined up. It will gently be seated by hand, and then the impaction device placed to fully seat and impact to engage and secure the peripheral taper lock.

Here, again, after irrigation by inspection one assures himself of full seating and lack of any injury to the implants.

This shows the fully seated Trident System in place after reduction of the hip.

[Slide]

This is the postoperative x-ray for the Trident System.

[Video presentation]

Finally, I would just present the case presentation. This is a 55-year old, 6'3", 230 lb. dentist. He received two total hips with alumina on alumina ceramic bearings at the age of 52. He works daily, walks the golf course two or three times per week. He is typical of the active and physically demanding patients in my practice who have received the alumina on alumina ceramic bearings. Thank you, Mike.

Clinical Data Summary

DR. MANLEY: Michael Manley again.

[Slide]

I will now present a summary of the clinical data. These data are based on the three-month update document sent to FDA. Panel members may refer to Amendment 4, Volumes 1 and 2 of their documents for reference. As the panel has the full data set, I will go through these data fairly rapidly.

[Slide]

To remind you, these are the three systems under test. System I has an alumina/alumina bearing. System II has an alumina/alumina bearing and the control system has a polyethylene liner with a cobalt chromium alloy head.

[Slide]

The randomization procedure is outlined fully in your documentation. The important point to note is the surgical site called the sponsor with patient identification etc., and day of surgery, and the randomly selected implant was then sent to the site.

[Slide]

the inclusion-criteria are also in your document. The important point here is that all of the patients in this study were non-inflammatory joint disease cases.

[Slide]

Investigational sites are listed. You will note there are only two of them with less than ten implantations.

A total of 515 implants were placed in each of the study arms.

[Slide]

Here is the number of cases with two-year follow-up. These are the data that we are presenting today. In System I there were 131 patients with two years of follow-up; in System II, 129; and in the control group, 119.

[Slide]

I have put some of these data as pie charts simply because it is easier to visually compare the data sets. This is diagnosis by system. You will note that in System I the majority of the patients have osteoarthritis. This is also true of System II and also of the control group.

[Slide]

Here is the demographic breakdown by age of the three systems. You will notice that the randomization procedure did, in fact, assign patients to every age decade from 21 to 75. The mean age of this study population is quite young for total hips, around 55 or a little less than 55.

[Slide]

Here are the demographics by gender for the three systems. You will note that in all three systems a majority of the patients were male. This is consistent with the literature for young groups of patients where the majority

of total hip patients happen to be male.

[Slide]

Let's quickly go through the results, firstly the clinical findings.

[Slide]

Here is the follow-up available for the study. You will note that in all three systems more than 90 percent of the patients are available for follow-up two years after surgery.

[Slide]

When we look at this group of patients and look at their Harris Hip Scores -- the preoperative score is shown here and the two-year data on the far right -- we see that there is a statistically significant increase in Harris Hip Score over that two-year period, and at the two-year period all three systems are equivalent.

[Slide]

This data set is the patients' own rating of their satisfaction of the hip system from the Hip Society scoring system. If you look at System II, you see that the patients are completely satisfied with that system. But when we scan through all of the data, we find equivalence between System I, System II and the control for increased function, decreased pain, less pain medication and satisfied patient.

[Slide]

A different type of patient satisfaction measure, this is the HSQ-12 scoring system from the Medical Outcomes Institute. Here are the preop scores for the three groups, and here are the postop scores at 24 months. You will note that there is a statistically significant increase in score. The three systems, however, are equivalent to one another at two years follow-up.

[Slide]

This is a very busy slide. This is operative site adverse events by category and by system. Let me take you through the top line first. The top line is alumina insert chips. We note that in System I two inserts were chipped at the time of insertion; two inserts in System II and, of course, the controls do not suffer from this problem. I will come back to the issue of insert chips again later.

If we look at the other adverse events, we find that Systems I, II and control are equivalent to one another, and these data are fairly typical of a total hip series in this sort of patient population.

[Slide]

The time course distribution of operative site adverse events shows that the majority of them in all three systems occurred within the first three months post-surgery.

[Slide]

The definitive endpoint, of course, of hip

replacements is revisions or reoperations. These data are shown on this slide. You note that for revisions and reoperations there seem to be less revisions and reoperations in Systems I and II compared to the control. For reoperations the data sets are equivalent to one another.

[Slide]

Here is a breakdown of these revisions. In System I, there was 1/140 revised; in System II, 2/140; and in the controls, 5/133, for a total number of 8 revisions.

[Slide]

Here is the reason for those revisions in System I. The one implant that was revised was a postoperative femoral fracture at nine months post-surgery. In System II, there were two revisions, one for deep joint infection at ten months post-surgery, and one for recurrent dislocation soon after surgery, at five days. The five revisions in the control group are, one for postoperative femoral fracture; one for leveling discrepancy; one for deep joint infection; and two for recurrent dislocation.

[Slide]

Now I would like to turn to the radiographic findings. The reviewer of the radiographic data was Dr. Peter Bonutti, from Effingham, Illinois. Dr. Bonutti has an academic appointment at the University of Arkansas. I

should note here that he reviewed all these radiographs in a blinded fashion.

[Slide]

Here is a sample radiograph from the ABC System I. This is in a 30-year old female. Here is the seven-week film and here is her film at two years follow-up. You notice that there are no lucent lines; no implant migration. This is consistent with a stable hip.

[Slide]

Here is a 32-year old male in System II, here at seven weeks follow-up and here at two years follow-up. We note in this particular instance that the surgeon chose to use bone screws with the acetabular components. Again, there are no lucent lines; no implant migration -- another stable result.

[Slide]

Finally, a control implant at seven weeks follow-up, and the two-year follow-up on the right. This is a 55-year old male. Again, the findings are no lucent lines, no implant migration and a-stable result.

[Slide]

This is the number of radiographs available for follow up. This is the percentage of radiographs from those patients that returned for their two-year clinical evaluation. So, more than 90 percent of those patients had

films that were evaluable for the radiographic review.

[Slide]

One of the failure criteria outlined in the study is femoral radiolucencies greater than or equal to 2 mm at two years follow-up. We see that in System I there is one patient with a radiolucency in zone 1 of the Gruen zones; in System II, one implant had a distal radiolucent line; and in the control group one implant also had a distal radiolucent line.

[Slide]

Cortical erosion is related probably to release of debris from the articulation. We see that in System I one patient was diagnosed as having cortical erosion in zone 1. There were no cases in System II. In the controls, one case had cortical erosion in zones 1 and 7.

[Slide]

Here is that particular case from the control group. Here is the seven-week film and here is the patient's two-year film. We see here an area of cortical erosion close to the resection level, and here also in the greater trochanter. This is the only case of this type in the control group.

[Slide]

Here is the case from System I. The cortical erosion was read to be here, within the greater trochanter,

at six-months follow-up although the reviewer said that at three years follow-up that now seems to be a radiolucency and not an area of cortical erosion at all. It is, however, reported as cortical erosion in your documents.

[Slide]

Turning to the acetabulum, again radiolucencies greater than or equal to 2 mm at two years follow-up, in System I there was one in the dome of the implant. There were none in system II and in the control group one patient had radiolucency superior to the cup.

[Slide]

If we look at stability using the criteria outlined in your document, there were no unstable implants at two years follow-up.

[Slide]

So, in summary for the ABC study at two years follow-up, here are the success/failure criteria for revision. There was one case in System I, two in System II and five in the control group.

Patients with Harris Hip Scores of less than 70 were also taken to be failures. There were two in System I, two in System II and three in the control group.

The other failure causes are equivalent to each other, and there were no findings, except there was one patient in System II who had a femoral component subsidence.

This was after a traumatic event following surgery.

[Slide]

The radiographic criteria we have presented suggest that these hip components utilizing the ABC and the control bearings are consistent with stable, pan-free hips.

[Slide]

The clinical criteria -- the Harris Hip Scores indicate that at two years follow-up System I and System II is at least equivalent to the control. For the overall success/failure rates these also suggest that System I and System II are at least equivalent to the control implants.

[Slide]

Here are the Kaplan-Meier survivorship curves for these three different systems. From these data, it seems that Systems I and II are at least equivalent to the control.

[Slide]

So, in conclusion from the ABC study, we believe the study demonstrates an equivalent performance of hips with the ABC bearings to that of hips with control-cobalt chromium polyethylene bearings at two years post-implantation.

[Slide]

I would like to now turn to the Trident arm of the study.

[Slide]

Just to remind you, this is the Trident System. The ceramic insert is backed with a shrunk-fit metal shell which is permanently fitted to the articulation, and then the metal shell is implanted into the acetabular component.

[Slide]

Here is a simple radiograph or a Trident case at six months post-surgery.

[Slide]

The investigators in this portion of the study were those investigators who had done the most ABC cases. This is the total number of ABC cases each investigator performed. Here are the controls and here are the numbers for Trident.

[Slide]

This is the total number of cases implanted throughout the time of the study. For the ABC System there were 173; System II, 177; Trident, 159; and 165 controls.

[Slide]

Here is the diagnosis breakdown for Trident. We see that the majority of the cases are osteoarthritis, as were the other three systems.

[Slide]

When we look at demographics by age of the Trident superimposed on the Systems I, II and control demographic

breakdown, we see that they are similar to one another, although no Trident implants have been implanted in the earliest age decade.

[Slide]

Breaking down gender demographics by system, we see once again that there is a majority of males in the Trident group, as there were in the other systems.

[Slide]

If we look at revision/reoperation by study system within 75 days of surgery, we see that for Trident there were no revisions or removals within this time period, as there were no System I removals within this early time period. The different systems are equivalent to one another. The same is true of reoperations. At 75 days follow-up the systems are equivalent to one another.

[Slide]

Operative site adverse events by study system, with Trident superimposed here on the other systems, we see that for Trident the intraoperative adverse events are less than they were for Systems I and II. The reason for this is that there are no cracks of the acetabular liner with Trident. The Trident articulation is completely protected by the metal backing.

[Slide]

So, here is the data for the operative site

adverse events by category for Systems I, II, control and Trident. If we go back to intraoperative insert chips, four of those occurred with System I in the entire group; four with System II. This does not happen with polyethylene. But none have occurred with Trident. For the other operative site adverse events, the different systems are equivalent to one another.

[Slide]

So, in summary for Trident, if we compare Trident to the ABC System, we have shown that the demographics are similar to one another, patient demographics for Trident and ABC.

Adverse events, there were less for trident than there were for ABC. Revisions within 75 days of surgery -- there have been none for trident; there was 0.3 percent for ABC, and reoperations -- there have been none for Trident versus 1.2 percent for ABC.

[Slide]

When we continue the comparison of the systems, the articulating bearing surfaces between Trident and ABC are identical to one another. We have shown that the stresses on the bone for Trident and ABC are equivalent, and both Trident and ABC meet FDA's standard for alumina femoral heads of 46 kN.

[Slide]

We looked at the risk/benefit analysis of Trident and ABC. One of the potential risks is breakage of the alumina insert. There have been none for ABC and none for Trident.

Disassembly of modular components -- none for ABC, none for Trident.

Revision options -- for ABC the revision option is the cementable polyethylene insert into the metal shell; for Trident the option is to use either a polyethylene insert which fits the shell or an alumina insert which fits the shell. This gives the surgeon greater scope if revision surgery is needed. As far as intraoperative chipping is concerned, there were 3.4 percent for ABC and none for Trident.

[Slide]

So, in summary, there are minimal risks, we believe, with ABC. We believe also there are fewer risks with Trident. The advantage of Trident is that the titanium sleeve protects the ceramic insert. The dual locking mechanism adds greater versatility to the system intraoperatively, and the system has multiple revision options.

[Slide]

I would like to now turn to the three questions raised by FDA with regard to these systems.

[Slide]

The first question relates to the issue of insert chipping.

[Slide]

There are four issues here that we have to address with insert chipping. The first is clinical consequences if a chip occurs. The second is implantation technique -- how do these chips occur and how are they prevented? The third is labeling, and the fourth is training and education. For the first two, clinical consequences and implantation technique, I would like to ask Dr. D'Antonio to address those two issues.

DR. D'ANTONIO: Thank you, Mike.

[Slide]

This slide shows an example of a typical case. There is a peripheral chip here. The fragment is laid inside, there, and just taped so that you can see the fragment inside.

Mike talked about 4 chips in that group of patients who had a minimum 2-year follow-up. In fact, there have been a total of 16 chips in the ABC study, 9 of which occurred in the study group and 7 of which occurred in the continued access group.

In this group of 16, 3 of the liners were left in place in the patient and continue to remain in the patient.

All of the others were replaced. Now, on x-ray review of all of these cases there is no evidence of any retained ceramic fragments. All of the implants are stable without signs of migration, reactive lines or lysis.

On a clinical evaluation, all but one of the patients is doing well. The one patient with a low Harris Hip Score has diffuse pain, including lower extremity pain and including pain in the operative side. The pain is of unknown etiology and x-ray review by four orthopedic surgeons has shown that the implants are well positioned and appear to be secure, without any adverse findings.

These cases have not resulted in an increased operative time, an increase in either the total intraoperative or postoperative complication rates of any of the study groups, and it is my opinion that if chipping does occur the additional risk to the patient is minimal as long as the ceramic liner is not left in a canted position within the metal shell. Chipping occurs at a very low rate and appropriate physician warning, as well as training, should address this issue in the future when this device is used.

I would like now just to go over the insertion technique to give you an idea of what we are talking about and how these occur.

[Video presentation]

This illustrates placing the ABC liner within the

shell, passing your finger around to make sure that it is seated by about 2 mm circumferentially all the way around. Then, the impactor can be placed and the taper lock secured.

I will now position this in a canted position. This canted position is extreme and, if you could imagine, it could be a lot less than this and create a small chip. That is canted and not fully seated. If you now apply pressure and try and force that into place, then a little peripheral chip will occur in this area. If, indeed, these do get canted, then simply tapping on the metal rim loosens them and you can then softly seat them with your index finger and then secure them with the peripheral taper lock.

DR. MANLEY: Michael Manley. I would now ask Beth Staub to address the issue of labeling and training and education.

MS. STAUB: While our initial instructions for use in the surgical protocol that accompanied the study devices did touch on the issue of proper alignment of the liner in the shell, there was no specific reference to chipping, which we were not aware-would be an issue at the time. We believe we can develop a program of labeling and surgeon education that will discuss the possibility of chips and provide surgical techniques, such as those discussed by Dr. D'Antonio, on how to avoid them.

DR. MANLEY: Thank you, Beth.

[Slide]

Let's turn now to question number two. This question relates to the Trident data and whether the seven-week data available from Trident could be representative of the two-year data from the ABC System. Again, Beth Staub should answer this question.

[Slide]

MS. STAUB: The FDA has published draft guidance identifying the least burdensome approach to premarket approval. We believe that the combination of mechanical and clinical data that we have provided on Trident adequately addresses any potential risks.

[Slide]

ABC and Trident are similar designs, use similar components and have identical bearings.

[Slide]

ABC and Trident have shown comparable mechanical performance to ultimate compression strength, axial fatigues and post-fatigue testing, off-axis fatigue testing, fretting testing evaluating the metal/metal interface, axial distraction and the bone/shell interface analysis.

[Slide]

Additionally, we have provided clinical results demonstrating equivalency of demographics, adverse events and 75-day revision and reoperation data between ABC and

Trident.

[Slide]

So, to echo Mike's comments from before, we believe there are minimal risks with ABC, even fewer risks with Trident. The titanium sleeve protects the ceramic insert. The dual locking mechanism adds versatility and provides intraoperative flexibility to the surgeons, and we have now multiple revision options with this system.

DR. MANLEY: Michael Manley.

[Slide]

Finally, I would like to address panel question number three, which is the issue of postmarket surveillance with the systems and, again, I would like to ask Beth Staub to address the issue.

[Slide]

MS. STAUB: Howmedica Osteonics proposes to continue to follow the subjects who have been involved in this study annually until the patients have obtained two-year follow-up. That would include following the 515 ABC and 114 continued access patients until the last patients from the original cohort reaches two years, giving us four-year follow-up on the early patients. We also intend to follow the 213 Trident cases until the last patient reaches two years, providing three-year follow-up on the early cases.

[Slide]

DR. MANLEY: So, in final summary, this radiograph shows a single patient who has a Trident bearing on the left and an ABC bearing on the right. We believe that data has shown that ABC bearings are safe and effective as compared to the control bearings, and we believe that the mechanical testing and the early intraoperative data with Trident also shows that these bearings will be safe and effective.

Thank you. That concludes our presentation. I would like to turn this back to Dr. Boyan.

DR. BOYAN: Thank you. I am going to ask the FDA to make their presentation now, and ask Peter Allen, the lead reviewer to come up and give his analysis of the preclinical and clinical application.

FDA Presentation

Preclinical and Clinical Information

MR. ALLEN: Good afternoon.

[Slide]

My name is Peter Allen, and I am a biomedical engineer in the Orthopedic Deices Branch of the Office of Device Evaluation at FDA.

DR. BOYAN: Mr. Allen, before you start. Sponsor, actually it is time for you to go back and be in the audience. Thanks. Okay.

MR. ALLEN: I am also the lead reviewer for this

PMA.

I would like to thank Howmedica Osteonics for their presentation this afternoon, and the panel for your attendance here today.

We are here to discuss the premarket approval application for the Osteonics ABC and Trident ceramic-on-ceramic hip systems. I will provide a brief review of the preclinical and clinical information in the PMA and Dr. Harry Bushar, of the Division of Biostatistics, will provide a review of the statistical data.

[Slide]

These hip systems are intended for use in patients requiring primary total hip replacement who are diagnosed with non-inflammatory degenerative joint disease, which is defined by the indications listed here.

[Slide]

The ABC System is available in two versions, referred to here as System I and System II. Both versions feature a ceramic-on-ceramic bearing couple. The bearing couple consists of an alumina ceramic femoral head and an alumina ceramic acetabular insert. it is this ceramic bearing couple that makes these systems investigational.

Both systems use commercially available Omnifit hydroxyapatite-coated him stems, and all components of both systems are intended to be implanted without cement.

The primary design difference between these two systems involves the exterior coating on the acetabular shells. System I features a titanium shell with an Arc-Deposited titanium coating beneath a plasma-sprayed hydroxyapatite coating. System II features a titanium shell with an Arc-Deposited titanium coating beneath a plasma-sprayed hydroxyapatite coating.

[Slide]

Like the ABC Systems, the Trident System also features a ceramic-on-ceramic bearing couple. It uses the same ceramic femoral head and Omnifit hip stem as the ABC Systems. All components of the Trident System are also intended to be implanted without cement.

The Trident represents the latest design iteration of the ABC Systems. The primary design difference between the Trident and ABC Systems involves the acetabular insert/shell interface. The Trident incorporates modifications to the insert locking mechanism that helps to eliminate intraoperative chipping of the ceramic insert, and improve the use and revisability of the device.

The Trident alumina ceramic insert is pre-assembled to a titanium alloy sleeve at the factory. This insert and sleeve assembly mates with the Trident acetabular shell via a taper lock fit. This metal-to-metal interference fit eliminates the potential for chipping of

the ceramic insert that can occur with the ceramic-to-metal interference fit of the ABC Systems.

The Trident acetabular shell is manufactured from titanium alloy and has an Arc-Deposited titanium coating beneath a plasma-sprayed hydroxyapatite coating, similar to the coating on the ABC System II shell.

[Slide]

The sponsor performed these preclinical mechanical tests in support of the ABC and Trident Systems. A detailed description of these tests and results was provided in the PMA. In addition, wear test data on the ceramic bearings was provided in a master file from the ceramic bearing supplier, CeramTec of Germany. FDA believes that the preclinical testing is adequate and has no further issues with it.

[Slide]

The next four slides depict the criteria under which the clinical data was collected and analyzed for the purposes of supporting this PMA.

[Slide]

The following primary safety and effectiveness data were to be collected at the designated follow-up evaluations until all patients reached the two-year study endpoint. Efficacy was to be based on Harris Hip Score, which includes pain and function components, and on

radiographic assessment. Safety was to be based on component revision events and overall adverse events.

[Slide]

Patients were considered a failure if they met any one of the following criteria at the two-year study endpoint. That is, a total Harris Hip Score of less than 70; a radiographic failure; or a revision of any of the device components.

[Slide]

A radiographic failure was defined as meeting any one of the criteria defined here.

[Slide]

Study success was defined as not detecting, as statistically significant, an increase of greater than or equal to 7.5 percentage points in the 2-year patient failure rates for Systems I or II over the 2-year failure rate for the control, and complication rates that are statistically no worse than the control.

[Slide]

I will now focus my review on the clinical data collected and analyzed for the ABC Systems. This will include the updated information provided in Amendment 4 to the PMA. I will then discuss the Trident data a little bit later.

[Slide]

The ABC System study was a randomized, prospective, controlled, multi-center trial with 515 cases enrolled at 16 sites. The PMA contains data on 413 cases who have either reached the 2-year study endpoint or were revised prior to their 2-year follow-up.

This PMA also contains data on 102 cases who have not yet reached the 2-year study endpoint. As a result, only their 1-year safety data has been examined by the FDA for the purposes of evaluating study success.

[Slide]

The 413 cases serve as a primary analysis group that supports the safety and efficacy analysis for this PMA. Of the 413 cases in this group, 140 cases were implanted with System I, 140 cases with System II, and 133 cases with the control system.

The control system is a standard metal-on-polyethylene hip that consists of the Howmedica Osteonics components listed here. All four components are commercially available for use in the U.S. The acetabular shell of the control system has the same titanium porous coating as the ABC System I shell.

[Slide]

With respect to the results obtained for the primary efficacy measures, here we have the Harris Hip Score results taken from the primary analysis group. A score

greater than 90 is considered excellent, 80-90 good, 70-80 fair, and below 70 poor.

As you can see from the first line, the mean preoperative scores were virtually identical for all three groups. At two years there is no significant difference in mean scores as all three groups are in the excellent range.

You will also note that there is no significant difference in the percentage of cases with scores less than 70. Remember that a score less than 70 is one of the patient failure criteria. Two cases from System I, two cases from System II, and two cases from the control system had scores below 70 at the two-year follow-up.

[Slide]

With respect to the previously defined radiographic failure criteria, one case from System II was defined as a radiographic failure due to progressive subsidence of the femoral component. No radiographic failures were detected for System I or the control system.

[Slide]

With respect to primary safety measures, here we have a summary of the revision and adverse event rates. This table includes all 515 patients enrolled in the clinical study including those 102 cases with less than 2-year data.

With regards to revision rates, the control system

demonstrated a slightly higher revision rate than the ABC Systems. Specifically, System I had one revision, System II had two revisions and the control system had five revisions.

Operative site and systemic complications appear comparable for all three groups. However, within the operative site interoperative complications we do find that among the ABC devices there were a few occurrences of intraoperative chipping of the ceramic inserts which contributed to their slightly higher intraoperative event rate.

[Slide]

Of the 172 cases implanted with System I, there were 5 reports of chipping of the ceramic insert during insertion of the device. That is, 2.9 percent of the cases experienced this event. There were 4 chipping events reported for the System II components, for an occurrence rate of 2.3 percent.

This chipping complication is unique to ceramic inserts due to the brittle nature of ceramic materials. The chipping is a potential concern because chipping of the ceramic insert, if undetected, could lead to catastrophic fracture of the insert postoperatively.

It should be noted that the chipped inserts reported on here were replaced intraoperatively with no further complications, and these patients were all doing

fine at their last evaluation.

[Slide]

Here we have the overall failure rates for each system based on the number of patients who have met at least one of the three patient failure criteria.

If we look at the overall patient failure rates for the three systems we see that the results are not significantly different based on the defined study success criteria. ABC System I had a 2.1 percent failure rate, System II a 3.6 percent failure rate, and the control system a 6 percent failure rate at the 2-year endpoint. Based on the failure rates and adverse event rates, both ABC Systems meet the defined study success criteria.

[Slide]

In addition to the primary and safety efficacy measures, the sponsor provided secondary data based on two patient satisfaction assessment tools.

The Hip Society Patient Satisfaction Assessment is directly related to the total hip process. The questions are taken from the Hip Society Clinical Evaluation. The percentages recorded here are the percentage of patients responding "yes" to these questions. As you can see, the results are comparable for all three systems.

The Health Status Questionnaire, (HSQ) -12 is a measurement of patient's general health which includes

physical and mental health components. It is based on a 100-point scale, with a higher score representing an improvement in health. The preoperative and 24-month mean scores are provided here and, again, you see that the results are comparable for the three systems both preoperatively and postoperatively.

[Slide]

After enrollment of the original 515 cases was completed, FDA approved a continued access study for an additional 336 ABC System cases. These cases were followed to provide additional safety information.

To date, 116 cases have been implanted. Data from 114 is included in the PMA. All 114 cases are out past 7 weeks, and 86 cases are out to their 1-year postoperative time point. The vast majority of these cases, 113, were implanted with System II. Only 3 cases were implanted with System I, as it appears the study surgeons have a strong preference for the hydroxyapatite-coated acetabular shells of System II.

Since most of the cases received System II, the adverse event safety information was pooled together. The adverse event rates were unremarkable in that they were comparable to the rates previously discussed for both Systems I and II and the control system. There were no reported revisions. However, 6 chipping incidents were

reported for the 116 cases.

Combining the continued access cases with the original group of cases receiving Systems I and II, the overall chipping rate for the ABC System inserts is 3.4 percent.

[Slide]

Now I would like to comment on the clinical study for the Trident system. The Trident System was added as an additional study arm to the ABC System IDE last year. Remember that the Trident is an updated design to the ABC System, with the main modification involving the locking mechanism between insert and shell.

[Slide]

The Trident arm is a non-randomized, prospective, controlled, multi-center trial for 213 cases, conducted at 6 of the original 16 ABC System study sites.

Patients implanted with the Trident were compared to the control system data collected in the original ABC System IDE. Trident study patients were evaluated using the same clinical protocol as the ABC System patients.

To date, 159 cases have been enrolled in this study arm, 157 of which are included in the PMA data analysis, and 135 cases have reached the 7-week postoperative evaluation time point and 27 cases have reached their 6-month evaluation time point. No cases have

yet reached the 1-year evaluation point.

[Slide]

As a result, clinical data on the Trident is preliminary at this tie as only a handful of cases have completed their 6-month evaluation.

In addition, no radiographic data has been provided for these cases due to the short postoperative follow-up times. If we look at the available 6-month results for both Trident and the control, we see that the average Harris Hip Scores are comparable for both systems.

The adverse event rate for the Trident is lower than the adverse event rate for the control at 6 months. Of particular note, there were no revisions reported for the Trident, and no occurrences of chipping of the Trident ceramic insert. In addition, the mean HSQ-12 score at 6 months is slightly higher for the Trident.

It is the sponsor's contention that, in addition to the preclinical mechanical testing and short-term safety data from the Trident System, the clinical data for the ABC Systems may be used to support the safety and efficacy of the Trident System. This is based on the use of the identical ceramic bearing surfaces, exterior shell geometries, and femoral components in both the ABC and Trident Systems.

[Slide]

I will now turn the floor over to Dr. Harry Bushar to discuss the statistical analysis. After Dr. Bushar's presentation I will provide a slide which summarizes the issues we would like you to think about during your discussion. I will then provide the specific panel question slides once we get into that part of your discussion. Harry?

Statistical Analysis

DR. BUSHAR: Thank you, Peter.

[Slide]

My name is Harry Bushar. I am the statistical reviewer for the Howmedica Osteonics ABC/Trident Systems PMA.

[Slide]

I am going to discuss the ABC System clinical trial which, of course, you have already heard about from Peter and the sponsor. I am going to focus on a few statistical points. The original study was prospective, controlled by Osteonics ABC System III, which is a standard hip system, and they do have 2-year follow-up on that. It was randomized between this control and 2 concurrent study arms, each getting about the same number of patients. These were Osteonics ABC Systems I and II which are, of course, experimental, and they each have 2-year follow-up. This was a multi-center study with 16 investigational sites.

[Slide]

The Trident System clinical trial was also prospective but, since it started late, it was historically controlled. Instead of doing a randomization, they decided to simply borrow the control from the previously completed Osteonics ABC System III. So the control was used for three different purposes, to compare to System I, System II and also Trident. This late study arm only has operative follow-up to speak of. In other words, they do not have any 2-year follow-up. This multi-center study used 6 of the 16 previous investigational sites to keep the results comparable.

[Slide]

In terms of follow-up, what we now have for System I is 172 hips, referred to as cases in most of the other presentation, with 140 hips out to 2 years. System II is similar, 177 hips with operative follow-up and 140 out to 2 years. With Trident there are 157 hips with operative follow-up and none out to 2 years. System III or control is 165 hips and 133 of these are out to 2 years.

[Slide]

I am going to look at safety first and I am going to focus in on the operative site intraoperative adverse event rates. The reason for doing this is that this is the category in which chipping occurred. Of course, you can see

the effect of that, even though I haven't broken it out as such. The event rates for System I and II are comparable, 11.6 in once case and 9.6 in the other. If you combine these, and there is no reason not to, there are similar results, and the demographics are very similar for System I and II. You get 10.6 percent. Then, if you look at Trident, you see that this is quite low, 2.5 percent and the control rate is 6.7 percent, somewhere in between the two.

[Slide]

What I have done here, I have looked at the difference of binomial proportions. So, I am comparing the results that were shown on the previous slide. What I am constructing are 90 percent confidence intervals. The reason for using 90 percent is I am going to focus in on one end of the other to try to make a statement as to what one can say when one compares Systems I and II combined to control.

What you could say from that interval is that Systems I and II combined are no worse than 9.1 percentage points higher than the control, and you could make that statement at the 95 percent confidence interval because you are just borrowing the upper end of the interval.

One can do a similar comparison of Trident to control, and there you can see that the worst that can occur is a 1.1 percentage point increase of Trident over control

at the 95 percent confidence interval.

The best way to look at the bottom interval is to look at the bottom part of the bottom interval, namely the 3.2 percent, and that shows that System I and II combined is at least 3.2 percentage points worse than the Trident, and that can be said with 95 percent confidence. So, it does appear that the Trident in the operative site intraoperative adverse event rates is doing something that has certainly reduced the chipping to zero.

[Slide]

As far as effectiveness goes, I am going to focus in on the failure, and failure was defined as revision, total Harris Hip Score less than 70, or radiographic failure. There was only one radiographic failure, and that was due to a progressive femoral component, subsidence which was greater than or equal to 5 mm.

[Slide]

The effectiveness failure rates are, for System I 2.1 percent, for System II 3.6 percent. Again, these are close and if you combine them you get 2.9 percent. The control rate was 6 percent.

[Slide]

I have done a very similar thing here. I have looked at the difference of binomial proportions, constructing 90 percent confidence intervals, and here one

would want to focus on the upper end of the interval. You can see that at worse the failure rate for System I is 1.9 percentage points greater than the control, with 95 percent confidence. System II is no worse than 3.6 percentage points greater than control, with 95 percent confidence. Then, if you combine the two and compare it to control you can see that the upper limit now drops to 1.3 percent so you are no worse than 1.3 percentage points greater for System I and II combined compared to the control, with 95 percent confidence.

That is it. I have finished. Thank you very much.

MR. ALLEN: Finally, we have our last slide.

[Slide]

This is a list of our discussion topics. I have individual slides for each of these that go into a little bit more detail, and we can go through those one by one when you are ready to address them. You also have a draft hard copy of these questions that was provided to you earlier, in Tab C of your white binder.

Anyway, here is a condensed version of the issues for which we are seeking your input: Number one is with regard to the chipping events reported with the ABC ceramic inserts; number two the short-term clinical data on the Trident System, and number three, the possible need for

longer-term clinical information for either or both device systems.

Thank you very much, and this concludes FDA's presentation.

DR. BOYAN: Thank you very much. I think now what we will do is have the lead reviewers from the panel give their assessments and then we will begin our official discussion. So, Dr. Li, would you please present your review of the preclinical data?

Panel Reviews

DR. LI: Sure.

[Slide]

These are just some of my comments that I have on the application. First, to kind of explain where I will end up, I thought I would tell you about how I got there.

One is to kind of look at the ceramic-on-ceramic historical overview prior to this particular device which Osteonics supplied in their application. The previous problems with ceramic-on-ceramic devices were probably in three categories: frank-fracture of the ceramic itself; a loosening usually of the acetabulum but often the stem as well; and impingement which led to other problems directly with the ceramic.

[Slide]

As far as fracture goes, after reading the

application and all the data, it appears that the problem is solved, and it is solved in a way that is with a scientific basis, basically in control of the grain boundaries by CeramTec of the ceramic, and followed by kind of an every product testing protocol where every particular product is actually load tested prior to sale.

This appears to have lowered the incidence of fracture of the ceramic to something probably less than the fracture of the femoral stems. So, I think the issue of fracture of the ceramic appears to be behind us as far as all the laboratory data goes.

[Slide]

However, interestingly enough, although the driving force for ceramic-on-ceramic is the reduction of wear, especially the avoidance or prevention of osteolysis, and although all the lab wear tests for ceramic-on-ceramic have always been essentially zero, there is osteolysis reported in the literature. The first case that I could find is back in 1991, which is a single case report in Acta Scandanavica. More recently, in '94, Shih reported 8/134 ceramic-on-ceramic devices that had osteolysis. Then in JBJS, January of '98, Yoon, in Korea, reported, amazingly, 66/103 ceramic-on-ceramic had osteolysis.

Now, it should be pointed out that these devices were a completely different design. The ceramics were

previous generations of ceramics. But I think it is important to note that just being a ceramic-on-ceramic device does not guarantee solutions of low wear and osteolysis.

[Slide]

The issue of loosening probably is the one that has the question mark in my head. The loosening in ceramic-on-ceramic devices, by and large, is aseptic loosening in the absence of osteolysis. Dr. Laurence Sedel, in France, probably has the longest history of this. In one particular case, out of 401 ceramic-on-ceramic devices, 44 of them became loose at the 15-year time period. In none of these cases was there osteolysis.

Again, I wish to point out that these devices were of a different design and different materials and after a 15-year follow-up, and really not a direct reflection, again, of the current device that we are talking about, but, again, wear has never really been the problem with ceramic-on-ceramic, with a few exceptions, it has always been loosening.

[Slide]

Kind of a fallout out of this is why do these patients loosen with these devices? Kind of a general consensus is it may have something to do with the design of the socket, many of which were threaded ceramic sockets.

Without a lot of analysis, we have always kind of pointed the finger at that, saying that must be the problem although there really hasn't been much follow-up data to actually demonstrate that that is it.

An interesting feature out of most of the ceramic-on-ceramic data is that if you break it out by age, the younger patients always do better in ceramic-on-ceramic devices. Of the 401 cases that we talked about of Dr. Sedel's, the green arrow indicates the survivorship at 15 years of those patients who were less than 50, and the white arrow indicates the survivorship of those patients that were older than 50. So, it is kind of the opposite of metal-on-polyethylene. In Metal-on-polyethylene, the younger you are, the worse you are. In ceramic-on-ceramic, it appears the younger you are, the better off you are.

[Slide]

So the question is although the fracture problem may be solved and osteolysis appears to be less frequent but certainly not necessarily at zero, the question is, is loosening solved? I think perhaps that is the feature that probably is going to make or break this device, and it is hopeful that the use of the cementless metal back liners will have addressed the loosening issue, although that is yet to be demonstrated in a long-term series.

[Slide]

This has been presented a couple of times but I want to talk a little bit about can you compare the different groups. Just as a quick reminder, perhaps for the fourth time that you have seen these slides, but I want to throw these up just as a kind of a reminder of how they are different either by material or by design. The ABC I and II essentially differ by whether or not there is an HA coating on the outside of the metal shell. The Trident is a little different. It has an HA coating but the key issue on the Trident, in my mind, is that the ceramic liner has essentially a shrink-fit titanium alloy sleeve that goes around the outside of it so you end up with a metal-on-metal junction in the shell rather than metal-on-polyethylene.

[Slide]

The other issue is that the Trident comes in one additional size, the 36 mm. The ABC I and II do not. I think the issue on the expanded sleeve is that, one, I think it was put in there to be a little more forgiving, if you will interface and it the installation was supposed to be easier, although I didn't really see anything that demonstrated that. Perhaps Dr. D'Antonio can actually comment on whether that is true and how they actually documented that it is easier.

I think the materials issue on the sleeve is that the way the sleeve is put on there, it is inductively heated

to kind of make the metal soft and expanded, and then they cool it and on cooling, it essentially clamps itself around the alumina ceramic, as I understand. Is that right? So, the titanium alloy sleeve is essentially in tension around the ceramic cup.

The only issue there that I could think of that might be a long-term issue is corrosion. Titanium is known to corrode, you know, at implant time of five or seven years, for crevice corrosion if you have like a mixed metal head on it. But, certainly, in this case where you have a piece of titanium that is under tension, the tendency to corrode is essentially higher depending on how much tension is applied. But, I didn't see any number in there for how much residual tension there is in the sleeve. It is not unrealistic if you have really high tension to increase the corrosion rate by a factor of five or ten quite easily. And, corrosion is not going to be seen in a short time period. When it occurs on stems, it usually comes at least at the five to seven year mark.

[Slide]

So, the Trident System is supposed to facilitate alignment, although I am not clear how the facilitation was documented, and it is supposed to be more forgiving in putting it in. Dr. D'Antonio called it canting. When I have handled these devices, it has always been kind of an

issue with me. It is possible, as Dr. D'Antonio showed, to put the liner in kind of off alignment. So, it is kind of stuck in there but it is actually not seated correctly and I have never been able to actually tap it out like he did in the movie. Sometimes the thing is wickedly in there and you have to work pretty hard to get it out. So, I am not sure how a general surgeon, or one that does these not so often, can actually guarantee that the liner is actually, in fact, aligned each and every time. And, if the Trident System actually helps to do that, it would have been helpful to have documented the benefit of that.

[Slide]

For the mechanical testing, especially in the absence of a guidance document, you have to compliment the applicants for doing extensive and actually very well done tests, and I really have no issues with those tests. I think the tests are appropriate and you passed them all well.

[Slide]

As a reviewer-you can't say that and stop. I think the only thing that I am a little surprised about, quite frankly, is that there is no independent wear testing done. Now, I did not have access to the actual CeramTec document that the applicants referred to but I guess my question, in the absence of seeing that data, is I am not

sure that comparison is appropriate. In other words, were the tolerances and the CeramTec thing the exact same tolerances that were used here, and what were the loading conditions and variations?

I am a little concerned also about testing of the devices -- if I had to comment on the testing, it is that they are done essentially under a single condition and not really addressing the wide variety of conditions that might be encountered surgically. For instance, on the metal and polyethylene case, things like abduction angle and anteversion, at least in extreme cases have been known to affect the wear and the question is did those same rules of thumb that govern metal-polyethylene surgical procedures, did those exact same rules hold for ceramic-on-ceramic? Maybe they do; maybe they don't. I just don't know.

[Slide]

So, in my opinion the load wear must be directly evaluated. In general, I think wear is a relatively poorly understood phenomenon. It is unclear to me how over probably the 25 or 30-year history of ceramic-on-ceramic in some people's hands the earlier ceramic-on-ceramic devices had wear; in other cases they don't. So, clearly, our understanding of wear in general is not all that well understood, and although I don't expect the results to be anything but sterling out of the laboratory given the